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PULMONARY FUNCTION IN ANKYLOSING SPONDYLITIS

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ABSTRACT

Ankylosing spondylitis has been said to be associated with an increased incidence of pulmonary infections and the commonest cause of death has been attributed to pulmonary insufficiency. Twelve patients with advanced ankylosing spondylitis, showing no evidence of cardiac disease, and who were less than sixty years of age, were investigated clinically and radiologically. Pulmonary function was evaluated with special reference to pulmonary gas exchange. Blood gas studies were performed at three levels of oxygen breathing and alveolar ventilation, diffusion, and venous admixture of blood evaluated.

Vital capacity was moderately reduced, total lung volume slightly reduced, and the residual volume was slightly increased in these patients. Timed vital capacity was normal, indicating that airway obstruction does not occur.

The restricted chest expansion and well maintained diaphragmatic excursion results in hyperventilation of the lower portions of the lungs and hypoventilation of the upper portions. This pattern of breathing has no significant effect on pulmonary gas exchange. A very mild arterial oxygen desaturation was observed in a minority of patients and CO_2 retention did not occur. Only one patient gave a history of recurrent pulmonary infections.

It is concluded that pulmonary complications are not a characteristic feature of ankylosing spondylitis and pulmonary insufficiency does not occur.

ACKNOWLEDGEMENTS

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THE PROBLEM

Recurrent pulmonary infections have been stated to be a characteristic feature of ankylosing spondylitis. The commonest cause of death in this disease has been said to be pulmonary insufficiency.

It is known that ankylosing spondylitis frequently causes reduction in the vital capacity, due to involvement of the thoracic spine and costovertebral joints, but little information on pulmonary gas exchange in this condition is available.

A study of pulmonary gas exchange at three levels of oxygen breathing was undertaken to delineate any defect which might exist.

INTRODUCTION

Ankylosing spondylitis is a chronic disease involving the sacroiliac joints, the small joints of the spine, and the adjacent soft tissues. The hip, knee, and shoulder joints are not infrequently affected, and other peripheral joints are occasionally involved.

The onset is characteristically in young adult life, the disease is usually progressive and the stigmata remain permanently. [10]

HISTORICAL NOTE AND TERMINOLOGY

The earliest known skeletal specimen of ankylosing spondylitis was described by Bernard Connor in 1691. [9] He described "An Extraordinary Human Skeleton" in which there was extensive ankylosis of the vertebrae and ribs. He recorded, "This person must have been immovable, that he could neither bend nor stretch himself out...and his breath must have been short." Pulmonary complications were thus suspected in the first description of this disease in the literature.

Sydenham first described the clinical features of the disease in the late 17th century. [40] By the end of the 19th century many clinical descriptions were reported and synonyms and eponyms for the disease were abundant.

The American Rheumatism Association[32] adopted the term Rheumatoid Spondylitis reflecting the prevalent American view that the disease is a spinal variant of rheumatoid arthritis. [35] Most British and

European authors hold that the diseases are separate entities and use the descriptive term ankylosing spondylitis. Since the question still awaits solution both terms are in common use, whilst most of the other synonyms have become obsolete.

AETIOLOGY AND PATHOLOGY

The aetiology is unknown. Various factors, including infectious processes, physical trauma, allergy, metabolic and hormonal disturbances have been implicated, but none of them have been accepted as the aetiological agent of the disease.[21, 10] More recently heredity has been considered an important factor and it is stated that ankylosing spondylitis is inherited as a simple autosomal dominant with slightly reduced penetrance.[24] Males are affected more than females in a ratio of 9 or 10 to 1,[42] but the ratio is lower in the familial form.[24]

There is surprisingly little information available on the pathology of ankylosing spondylitis.

Blumberg and Ragan[10] state that during the period 1906-1956 over 10,000 autopsies were performed at the Department of Pathology of the College of Physicians and Surgeons, Columbia University, and that the files contain no cases of rheumatoid spondylitis (or variants of this name) recorded either as a pathological or clinical diagnosis. Only one biopsy of sacroiliac joints, which was reported as negative, was present among 160,000 biopsies included in the file.

The modern view of the pathology of the disease is that the diarthrodial joints of the spine and the pelvis, the costovertebral joints, the costotransverse joints, and occasionally the symphysis pubis, the

manubriosternal joint and other peripheral joints are involved in an inflammatory process similar to that seen in peripheral rheumatoid arthritis.[26] Cruickshank[14] states that the process differs from rheumatoid arthritis in that the end result is bony rather than fibrous ankylosis. Ossification under the ligaments of the spinal column in the outer fibres of the annulus fibres also occurs and in the late stage of the disease produces the highly characteristic radiologic appearance known as the "bamboo spine." Ossification at the periphery of the intervertebral discs and extension of the vertebral spongiosa through the central part of the discs, so that the involved spine resembles a long bone has been reported,[37] but is extremely rare; usually the intervertebral discs appear normal and the vertebral bodies are not usually involved except for secondary osteoporosis.

Cruickshank points out that joints can react only in a limited manner to exciting agents, and that the similarity of histopathology in ankylosing spondylitis, rheumatoid arthritis, lupus erythematosis and non specific tenosynovitis should not be taken to imply a common aetiological agent.[15]

It is generally agreed that bilateral involvement of the sacroiliac joints is by far the commonest early feature of the disease and that detailed radiological studies of the sacroiliac joints are mandatory in suspected ankylosing spondylitis.

The incidence of involvement of the costovertebral and costotransverse joints is of particular importance in the present study, but due to the difficulty of demonstrating these joints radiologically few

references are available. Mowbray[39] and his group reported that radiological changes were present in the costotransverse joints in 58% of early and in 88% of advanced cases. This finding is supported clinically by the fact that reduced chest expansion is a highly characteristic feature of ankylosing spondylitis.[29]

The peripheral joints are involved in approximately 60% of the patients.[10] The hip joints are affected in 15%, and is a frequent cause of disability.[33] In contrast to rheumatoid arthritis the joints of the hand and wrist are rarely involved whereas the larger joints of the limbs are involved frequently.

Recurrent iritis, which occurs in 25-50% of subjects, may be the only reason for hospital admission, and on occasion may be the presenting symptom of the disease.[10]

It is now accepted that there is a form of heart disease which is peculiar to ankylosing spondylitis. Aortic incompetence is the main feature of the condition. The mitral valve is usually intact and the aortic valve shows thickening and rolling of the free edge, while commissure interadherence does not occur.[47] The aetiological nature of this aortic valvular disease is not known. Graham[23] found the incidence of aortic disease in ankylosing spondylitis to be 4.6%.

CLINICAL FEATURES

The clinical features of ankylosing spondylitis are variable reflecting the extensive pathology of the disease. Hart and his group[31] state that the four cardinal diagnostic features are:

1. spinal stiffness;
2. diminished thoracic expansion;
3. elevated E.S.R.;
4. X-ray changes of the sacroiliac joints.

Hart[30] found pain and/or stiffness in the lower back and buttocks to be the initial symptom in 73.4% of 184 cases. Characteristically the pain occurs in the early hours of the morning and frequently causes the patient to get out of bed and walk around to obtain relief.[33] Burrows[11] stated it was "surprising that so distinctive a disease was not generally recognised sooner," and this delay in diagnosis is emphasised by Swezey and his group.[54]

In a minority of patients the onset may be in the peripheral joints.[41] Occasionally pain in the heels may be the first symptom, and calcaneal spurs or periostitis may be seen radiologically.[16]

The disease is usually progressive and may affect the entire spine. The course is commonly interrupted by periods of remission, but ultimately the symptoms become more constant.[33]

Kyphosis is the most common deformity, however it varies greatly as to time of onset and severity. It results in slight loss of height. Forestier observed kyphosis in 68% of 200 patients.[20]

Thoracic spine involvement is common and chest expansion is reduced in the great majority of patients, being less than 2.5 cms. in over 50%.[29] Hart gives the following description of thoracic symptoms:

> Difficulty is experienced in moving the chest wall; tightness is noted in the ribs and muscles of the thoracic cage, more particularly anteriorly, but also in the flanks; the chest aches and feels stiff and immobile and the patient cannot fill his chest satisfactorily on deep inspiration.[29]

He states that the dyspnoea is secondary to a feeling of thoracic stiffness, and is "quite unlike that noted in cardiac or pulmonary disease."[29] Chest pain occurs commonly after coughing or sneezing. Hamilton drew attention to the impairment of the cough mechanism, due to loss of mobility of the costovertebral joints, and stated that episodes of pleuropulmonary disease are frequent and recurrent in ankylosing spondylitis.[27] Recently, Wilkinson and Bywaters[59] observed no difference in the incidence of pulmonary complications between 212 patients with ankylosing spondylitis and 253 patients with rheumatoid arthritis. Travis and his group[55] state "earlier reports attempting to shew a relationship between rheumatoid spondylitis and the development of pulmonary infections are based on clinical impressions and lack convincing comparative evidence."

There has been little study of mortality in ankylosing spondylitis, but a recent report indicates that the disease does not shorten life.[10] Blumberg and Ragan's observation that 80% of patients with disease of approximately 25 years' duration are regularly employed indicates that, functionally, these patients do remarkably well.[10]

METHODOLOGY

SELECTION AND CLASSIFICATION OF PATIENTS

All patients studied fulfilled the following criteria:

1. Definite clinical and radiological features of ankylosing spondylitis were present.
2. Chronicological age was less than 60 years.
3. There was no evidence of cardiac disease clinically or radiologically.
4. Radiological changes were present in the thoracic-lumbar spine as well as in both sacroiliac joints.

This method of selection excluded early or doubtful cases, and the possibility of complication of the pulmonary function results by old age or heart disease was eliminated.

CLASSIFICATION

The patients were classified on a severity basis by the radiological method outlined by Rogan, Needham, and McDonald.[46] This classification is:

+	Changes limited to sacroiliac joints.
+ +	Early changes in spine as well as in sacroiliac joints.
+ + +	Well marked changes in the thoracic and lumbar spine, with some evidence of ankylosis, as well as marked changes in the sacroiliac joints.

+ + + + Gross changes in sacroiliac joints and thoracic and lumbar spine.

CLINICAL DATA

All patients had received one or more courses of radiotherapy and had been instructed in some type of exercise programme. Most patients had received phenylbutazone during the course of their disease. The medical record of each patient was studied. The history was retaken and brought up to date. A complete physical examination was performed. Recent radiographs of the spine and chest were available in all patients. An electrocardiogram was obtained in all instances.

LUNG VOLUMES AND SPIROMETRY

The Godart Pulmotest, Model 1. A. 7000, was used. (Figure 1.).

Functional Residual Capacity. This was determined by the closed circuit helium technique.[5, 36] The patient was seated comfortably and allowed to adjust to the mouthpiece and spring nose-clip for at least five minutes. The measurement commenced at the end of a normal expiration, and readings were taken every 30 seconds. The point of equilibrium was determined by obtaining three consecutive identical concentrations of helium, and after a minimum period of five minutes.

Expiratory Reserve Volume. This was obtained by having the patient expire maximally after a normal expiration, and the test was repeated until reproducible values (within 50 ml.) were obtained, the largest value being recorded.

Residual Volume. The residual volume was obtained by subtracting the expiratory reserve volume from the functional residual capacity.

Forced Vital Capacity and Forced Expiratory Volume $_{0.5 \text{ seconds}}$.

This was measured by having the patient take a maximal inspiration and without hesitation to expire fully with maximal force. The total volume expired was the forced vital capacity (F. V. C.). The test was repeated until reproducible values (within 50 ml.) were obtained and the largest value recorded. The volume obtained in the first one-half second of this procedure was the Forced Expiratory Volume$_{0.5 \text{ seconds}}$ (F. E. V.$_{0.5}$) and here again reproducibility within 50 ml. was required and the largest volume recorded.

Maximum Ventilatory Capacity. The test was performed with the patient standing and the mouthpiece supported by the operator. The maximum ventilatory capacity was measured over the 15 second period giving the largest volume. The test was repeated after a ten minute resting period and the highest value taken.

Normal Values. The values of Baldwin and his group[4] were used. Despite the fact that Baldwin's values are for the supine position, little difference occurs when the patient assumes the sitting position.[12] Normal values using height as a separate factor, rather than surface area, were not suitable due to the loss of height resulting from spinal ankylosis.

PULMONARY GAS EXCHANGE

Principles of the Method. Four main types of pulmonary gas exchange defect are recognized:

1. Alveolar Hypoventilation.
2. Diffusion Defect.
3. Intrapulmonary Right to Left Shunting of Venous Blood.
4. Altered Ventilation - Perfusion Ratios.

1. Alveolar Hypoventilation.

This is defined as a decrease in alveolar ventilation in relation to the O_2 consumption of the patient, and is always associated with CO_2 retention and arterial O_2 desaturation. CO_2 retention is measured by increased arterial and alveolar CO_2 tension. There are many causes of alveolar hypoventilation, and they can be classified as follows:[13]

(1) Depression of the respiratory centres.

(2) Interference with neural conduction or with neuromuscular transmission to the respiratory muscles.

(3) Diseases of respiratory muscles.

(4) Limitation of movement of thorax.

(5) Limitation of movement of lungs.

(6) Parenchymal pulmonary disease.

2. Diffusion Defect.

Defective diffusion occurs when there is an abnormal barrier to the passage of O_2 from the alveolar gas into the pulmonary capillary blood. The tissue barrier across which the respiratory gases normally diffuse comprises the alveolar membrane, the interstitial fluid, the capillary membrane, the plasma, and the erythrocyte membrane. These structures are often considered collectively as the alveolar-capillary

membrane. The diffusion capacity of a gas is defined as the number of ml. of the gas which diffuse across the alveolar-capillary membrane per m.m. Hg. mean pressure difference per minute. Abnormality of the alveolar-capillary membrane which results in impairment of diffusion is known as alveolar-capillary block. Alveolar-capillary block occurs in a variety of conditions, including Boeck's sarcoidosis, asbestosis, pulmonary scleroderma, interstitial pulmonary oedema, and terminal bronchiolar carcinoma.[3] A decrease in the number of patent capillaries such as in multiple small pulmonary emboli results in decreased diffusion capacity by reduction of the effective diffusion surface area.

3. Intrapulmonary Right to Left Shunting of Venous Blood.

This can result from:

(a) Normal shunts through bronchial veins.

(b) Abnormal anatomic right to left shunts through

(i) pulmonary aneurysms,

(ii) angiomata,

(iii) through capillaries of non-ventilated alveoli, as in complete bronchial obstruction.

4. Altered Ventilation-Perfusion Ratios.

Alterations of the normal ratio of alveolar ventilation to pulmonary capillary blood flow result in abnormalities of pulmonary gas exchange.[17] If perfusion is reduced out of proportion to ventilation, (reduced ratio), this results in an increased physiological dead space;

if ventilation is reduced relative to blood flow (increased ratio), increased venous admixture of arterial blood occurs. Altered ventilation-perfusion relations occur in a variety of pulmonary diseases and represent the most frequent causes of anoxaemia in clinical medicine.[13] In chronic obstructive pulmonary emphysema altered ventilation-perfusion ratio is the predominant abnormality of pulmonary function.[58]

It is important to realize that arterial O_2 desaturation can exist in the absence of CO_2 retention. This is due to the fact that compensatory hyperventilation of normal alveoli can prevent CO_2 retention, but due to the shape of the oxyhaemoglobin dissociation curve cannot correct arterial O_2 desaturation.

Differentiation of Pulmonary Gas Exchange Defects. These four defects of pulmonary gas exchange may be differentiated by determining alveolar and arterial O_2 and CO_2 tensions at three levels of oxygenation and calculating the A-a oxygen tension gradients in each case.[34,44,45] Three suitable levels of inspired oxygen are, room air, 10-14% O_2, and 100% O_2.

The differentiation is as follows:

Alveolar Hypoventilation. If alveolar hypoventilation is present, arterial O_2 desaturation and CO_2 retention with normal A-a gradient will be found on room air breathing. A normal A-a gradient will be found at all three levels of oxygen breathing, therefore if an abnormal A-a gradient exists it must be due to some other cause.

Diffusion Defect. Impairment of diffusion of oxygen is shown by a wide A-a gradient on room air breathing; this gradient widens on inhalation of the low (10-14%) oxygen. As CO_2 diffuses across the alveolar-capillary membrane 20 times

more readily than oxygen, retention of CO_2 due to impaired diffusion is not compatible with life and for this reason CO_2 retention is not a feature of diffusion defect in clinical medicine. Low levels of inspired oxygen minimise the effects of venous-arterial admixture and this fact is utilised to distinguish between diffusion defect and venous-arterial admixture.[34]

Intrapulmonary Right to Left Shunting of Venous Blood. In the normal lung breathing 100% oxygen will result in 100% saturation of the arterial blood; in addition the physically dissolved oxygen will increase from the room air level of 0.29 mls. % to approximately 2.0 mls. %. A shunt of 2% of the cardiac output results in a decrease in the physically dissolved oxygen of only 0.1 mls. % so that a significant shunt may be present with the arterial saturation remaining at or above 100%. For this reason direct measurement of the arterial pO_2 by modern polarographic techniques[53] is a much more sensitive method of detecting shunts, and the A-a gradient on breathing 100% oxygen can be taken as a measure of the shunt.[7]

Altered Ventilation Perfusion Ratios. The large A-a gradient present in this defect when breathing room air, is abolished by the inhalation of 100% oxygen, as even minimally ventilated alveoli eventually attain an oxygen tension approaching atmosphere pressure, thus distinguishing the defect from an anatomical shunt.

Technique. The patient, wearing a hospital gown, was made as comfortable as possible in the supine position. The majority of patients required several minutes to achieve a comfortable position; they often

requested two pillows to support the head and neck as they were uncomfortable lying flat. The procedure was explained to the patient in simple terms and he was encouraged to relax as much as possible. The skin and subcutaneous tissues in the region of the femoral artery below the mid inguinal point were anaethetized with 2% procaine. The femoral artery was punctured with a Cournand needle. The stylette was inserted when the needle was well situated in the lumen of the artery as judging by the free pulsatile flow of arterial blood.

The mouth piece was inserted and several minutes allowed for the patient's adjustment. The patient breathed through a Rudolph two way valve and a spring nose clip occluded the nostrils. A small fraction of the expired air was drawn through a Godart Capnograph and the respiratory rate measured continuously. When the patient was breathing quietly and considered to be in a stable state the expired air was collected in a Douglas bag for four minutes. Midway through the collection arterial blood samples were withdrawn into heparinized Luer-lok syringes. Each syringe was capped immediately, care being taken to prevent the entry of air, and agitated manually to ensure complete mixing of the heparin.

The mouth piece was removed after the collection of expired air and cleansed of any accumulated saliva.

The procedure was repeated with the subject breathing 10-14% oxygen from a large balloon attached to the inspiratory side of the valve. (Figure 2.). The arterial oxygen saturation was monitored using the Waters Ear-Oximeter Model XP-65A. When the subject

reached a steady state as judged by a stable oximetry reading, and after a minimum period of 20 minutes, the expired air and arterial blood samples were collected in the same manner as for room air breathing.

The procedure was repeated with the patient breathing 100% oxygen from the balloon. Expired air and arterial blood samples were collected after 30 minutes.

The mouth piece and the Cournand needle were removed and direct pressure over the femoral artery at the puncture site was maintained for five minutes to prevent haematoma formation.

No untoward effects were encountered during or after the procedure except in one patient who developed a moderate haematoma of the thigh which resolved within several days.

Methods of Analysis and Calculation. The oxygen and CO_2 content of the inspired and expired gases were measured with the Scholander gas analyzer.[48] The volumes of the expired gases were measured with a Thomas laboratory gas meter, and adjustment made in each case for the volume extracted by the Capnograph. The oxygen capacity and content, and CO_2 content, of the arterial blood were measured by the manometric method of Van Slyke and Neill.[56] The pH of the arterial blood was determined by the micro technique of Astrup.[2] (Figure 3.). The arterial pO_2 was calculated from the Severinghaus nomogram.[49] (Figure 4.) Arterial p CO_2 was calculated using the Van Slyke and

Sendroy line charts.[57] The whole blood buffer base was calculated from the Singer-Hastings nomogram.[51] The alveolar p O_2 was calculated from the alveolar air equation,[13] assuming the alveolar p CO_2 to be identical with the arterial p CO_2.

The physiological dead-space was calculated from the Bohr equation,[13] and the ratio of physiological dead-space to tidal volume determined in each case. Alveolar ventilation was calculated using a conventional equation.[13]

As direct measurements of the arterial p O_2 were not made, values for 100% oxygen breathing could not be calculated from the Severinghaus nomogram; this is due to the sigmoid shape of the oxyhaemoglobin dissociation curve. The volume of oxygen physically dissolved in the arterial blood in these samples was obtained by subtracting the capacity volume from the measure volume of oxygen.

The complete method of calculation and the equations used are shown in Appendix I utilizing the results of Case 10.

Experimental errors of the techniques used and their significance are discussed in Appendix 2. Statistical data are given in Appendix 3.

Figure 1. Photograph of the Godart Pulmotest

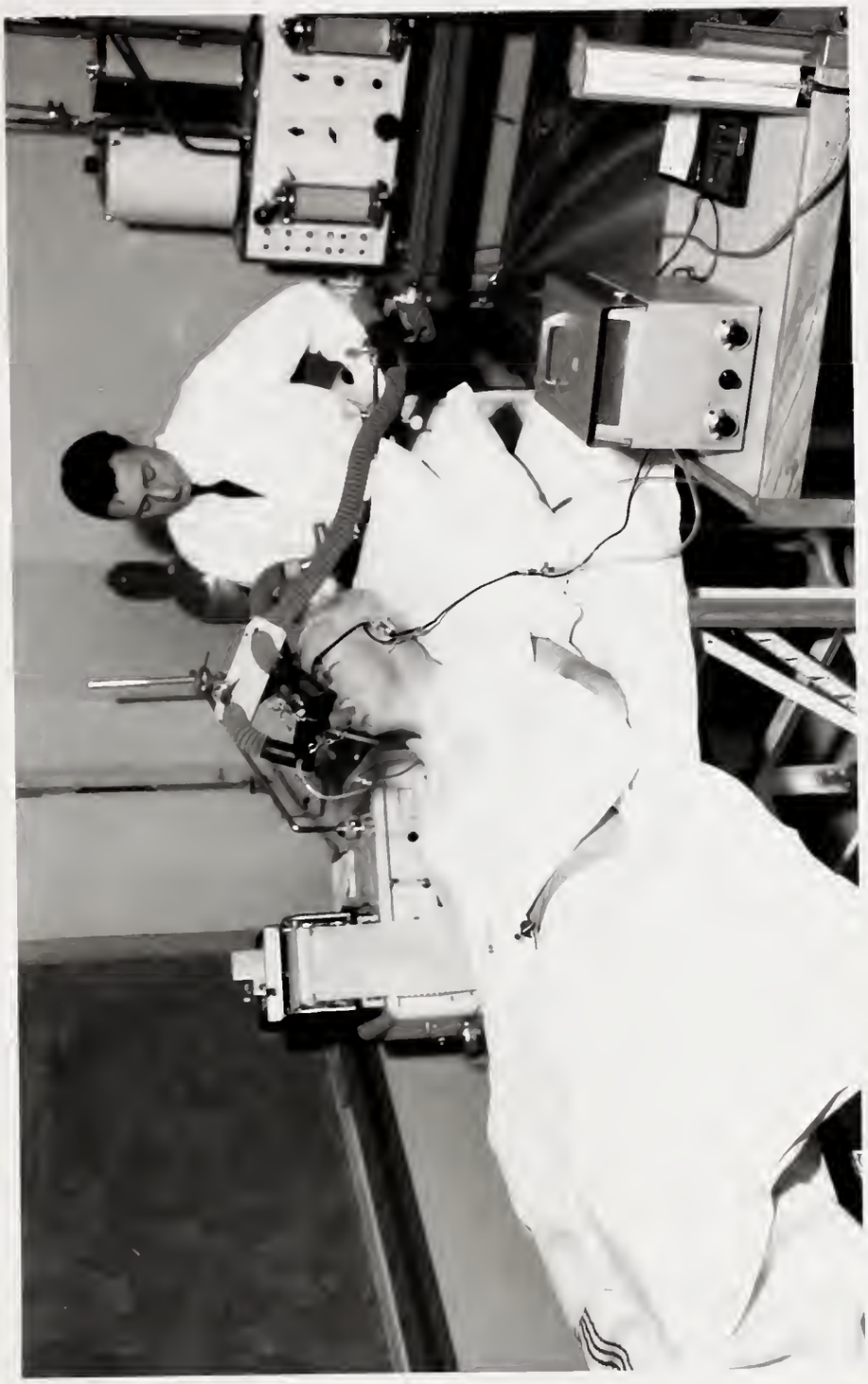

Figure 2. Photograph of Apparatus as used in Pulmonary Gas Exchange Measurements

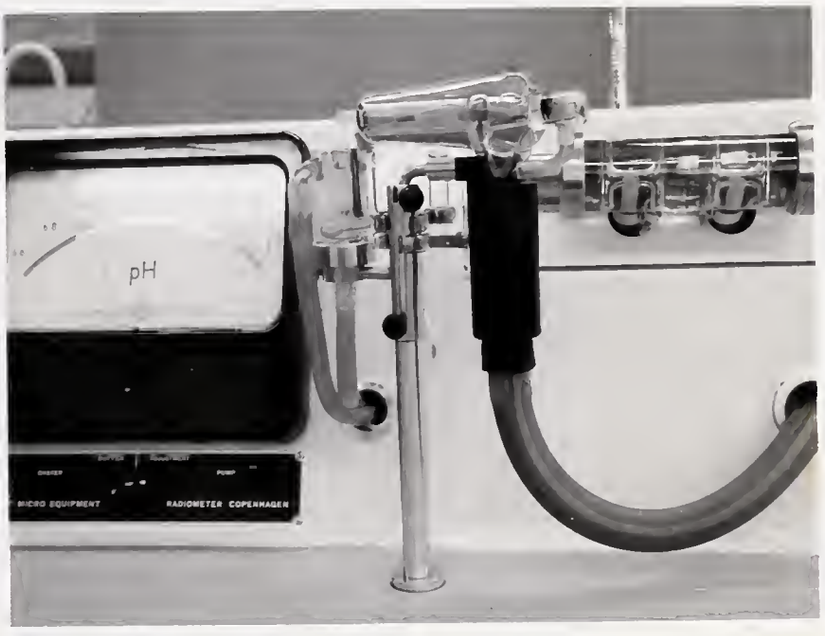

Figure 3. Photograph of the Astrup Micro Equipment, Type AME 1

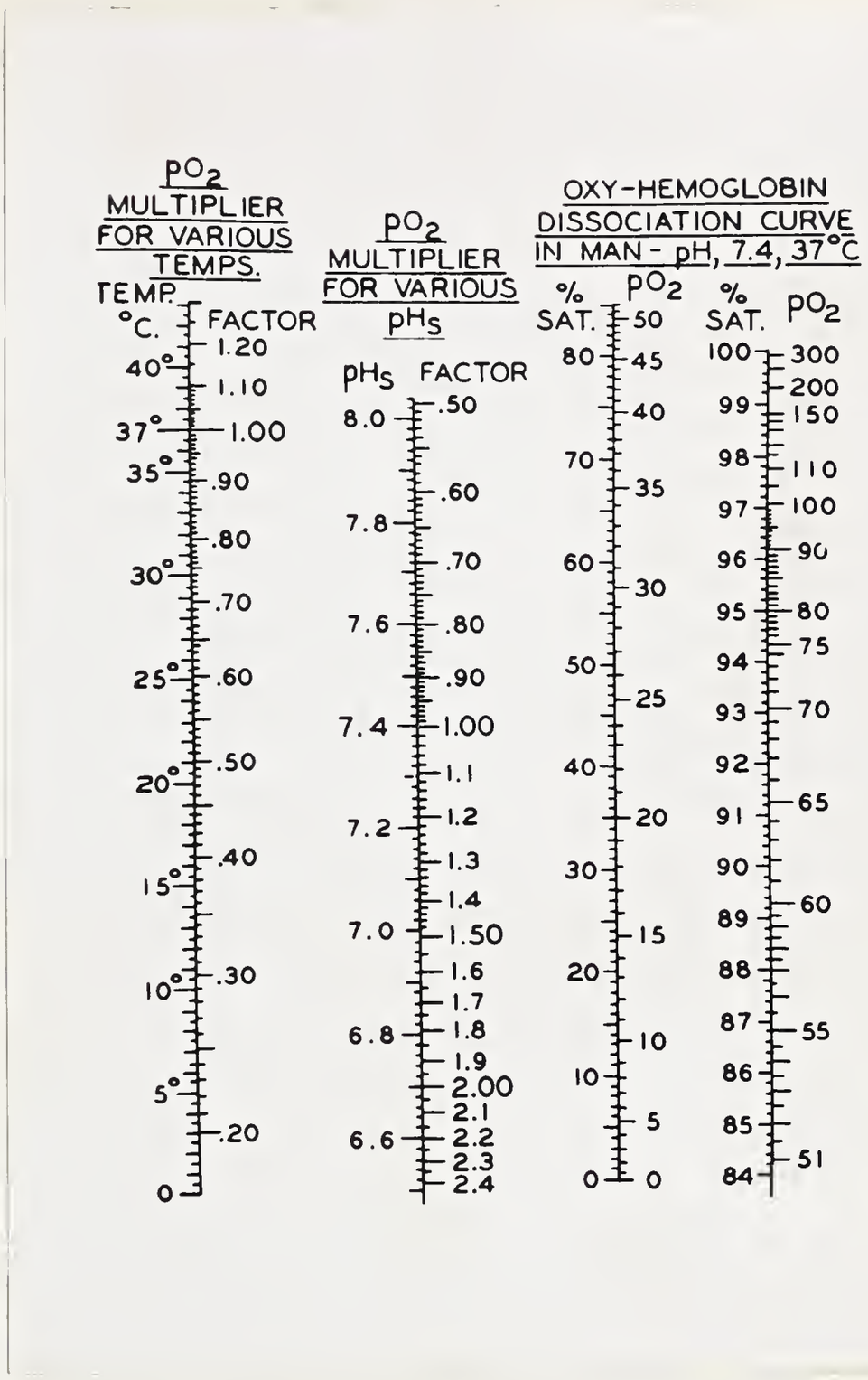

Figure 4. Photograph of Severinghaus Nomogram for Arterial Oxygen Tension.

RESULTS

A total of fourteen patients was studied. In two patients, S.L. and G.T., a steady state could not be obtained when they were breathing through the mouth piece; their respiratory quotients were 1.34 and 1.18 respectively, which are unsuitable for pulmonary gas exchange calculations, as the equations used assume a steady state. Neither of these patients had any complaints referable to the respiratory system and had arterial oxygen saturations of over 95% as determined by the ear oximeter. These patients were assumed to be unable to relax for the procedure and the results are not included in the series.

Pulmonary ventilation and gas exchange studies were successfully completed on twelve patients and the results, including clinical features, are shown in Tables 1 to 4.

CLINICAL FEATURES (Table 1).

The majority of patients had slight or moderate kyphosis of the thoracic spine, although none had the severe kyphosis which can occur in advanced untreated disease. Ten patients had advanced disease and the remaining two patients had milder but established ankylosing spondylitis. The duration of the disease ranged from seven years in Case 10 to twenty-seven years in Case 5, and the mean duration was eighteen years.

Case 11 had definite evidence of chronic bronchitis, and was hospitalized for two weeks during the research programme. A diagnosis of pneumonitis superimposed on chronic bronchitis was made; he responded well to antibiotic therapy and the pneumonitis cleared. A bronchogram showed no evidence of bronchiectasis. He was a heavy smoker and lived in the bush where he earned a living as a trapper. None of the other patients admitted to production of purulent sputum, and none gave a history of frequent respiratory tract infections. All patients were regularly employed and self supporting except Case 6 who was an alcoholic. Six weeks from the time of blood gas studies he was admitted to hospital with a suspected apical pulmonary carcinoma. Case 3 was treated with steroids for a three-year period and they were discontinued six months prior to the date of the pulmonary gas exchange studies.

The chest X-rays revealed normal lung fields in nine patients, while there were increased bronchovascular markings in three patients (Cases 1, 11 and 12). Electrocardiograms were reported as normal in all cases.

LUNG VOLUMES AND VENTILATION (Table 2).

The total lung volume had a mean value of 87% for the group. Two patients (Cases 1 and 7) had greater lung volumes than the predicted normal values. The lowest value observed was 69% (Case 4). The vital capacity was reduced in all cases with a mean value of

72.7%. The chest expansion was reduced in all cases with a mean value of 2.48 cms. which is less than 50% of the normal value of 6 cms. Vital capacity changes are similar in amount and direction to those of chest expansion. The ratio of residual volume to total lung volume, which is normally around 25%, had a mean value of 36.7%. The ratio of observed to predicted residual volume had a mean value of 129.6%, seven of the patients having significantly increased values (Cases 1, 2, 5, 6, 7, 10 and 11) while two patients (Cases 3 and 4) had reduced values. The forced expiratory volume, timed over the first half-second of expiration had a mean value of 62.7% which is normal,[38] and the lowest value was 53% (Case 11) indicating that no significant degree of airway obstruction was present in any of the group. End tidal alveolar pCO_2, as determined by the Godart Capnograph, was within normal limits in all cases, showing that CO_2 retention was not present, and this finding was verified by the arterial blood results.

HAEMOGLOBIN AND HAEMOTOCRIT

The mean value of haemoglobin was 13.11 G. and the haematocrit had a mean of 40.5% indicating a mild anaemia existed in the group as a whole, and seven patients (Cases 3, 5, 6, 8, 9, 10 and 12) had haemoglobin values of less than 14.0 G.

PULMONARY GAS EXCHANGE (Tables 3 and 4).

The arterial CO_2 content, pCO_2, pH and whole blood buffer base

were within normal limits in every instance. The arterial oxygen saturation had a mean value of 95.5% which is normal, and Case 6 had the lowest value of the group which was 92.6%.

The A-a gradient on room air breathing had a mean value of 8.4 mm.Hg. which is normal. Case 9 had a gradient of -2 m.m.Hg. which is due to experimental error, as the arterial pO_2 can never be higher than the alveolar pO_2. Accepting 12 m.m.Hg. as the upper limit of normal for the A-a gradient, only three cases have elevated gradients (Cases 6, 7 and 9). Case 6 has the highest gradient of 27 m.m.Hg. and Cases 7 and 9 had gradients of 15 m.m.Hg. and 23 m.m.Hg. respectively. None of these three values is greatly abnormal, and it is noteworthy that Case 6 may have had early apical pulmonary carcinoma when the studies were performed; this patient had the lowest haemoglobin of the group and this may have also contributed to the increased gradient.

The A-a gradients of the remaining nine patients were within normal limits and furnish proof that no arterial oxygen desaturation exists.

The alveolar ventilation had a mean value of 2.78 litres per minute per square metre of body surface area and this is within normal limits; the highest value was 3.36 litres in Case 2 and this is still within normal limits.

The ratio of physiological dead-space to tidal volume was elevated in every patient, with a mean value of 0.403 which is appreciably above 0.30, the upper limit of normality. This finding is diagnostic of increased physiological dead-space; that is a high ventilation-perfusion ratio. The respiratory quotients were within the range 0.78 - 0.96, with a mean value of 0.844, and were satisfactory for pulmonary gas exchange studies.

The low oxygen breathing studies showed normal A-a gradients in all patients and on this basis there was no evidence of a diffusion defect in any of the subjects.

Breathing 100% oxygen resulted in a complete arterial oxygen saturation in all subjects, thus eliminating the possibility of any large anatomical shunts in the group.

The dissolved oxygen had a mean value of 1.54 ml. % and this furnishes further evidence that no significant degree of anatomical shunting exists in any subject.

TABLE I. CLINICAL DATA

Case	Age (Years)	Height (Inches)	Weight (lbs.)	Body Surface Area (sq. metres)	Duration of Symptons (Years)	Radiologic Classification	Chest X-Ray	Respiratory System - History and Clinical Features
1. R. E.	34	68	167	1.89	15	+ +	slightly increased markings.	Heavy smoker; chronic cough; Mucoid sputum; Chronic chest pains.
2. S. T.	24	69	142	1.78	12	+ +	clear	nil
3. J W.	37	65	143	1.70	13	+ + +	clear	nil; steroid therapy for past 3 yrs.
4. J. E.	44	66	166	1.84	19	+ + + +	clear	Pneumonia 20 years ago; no symptoms at present.
5. G. F.	53	64	142	1.68	27	+ + + +	clear	nil
6. H. B.	46	67	134	1.69	23	+ + + +	clear	Heavy smoker; chronic cough.
7. M. T.	40	70	165	1.91	21	+ + ++	clear	Recurrent chest pains.
8. O. R.	35	65	134	1.67	17	+ + + +	clear	nil
9. P. T.	41	73	210	2.18	20	+ + + +	clear	Chronic chest pains.
10. J. M.	31	69.5	124	1.68	7	+ + + +	clear	nil
11. S. B.	40	68	120	1.63	21	+ + + +	Increased markings.	Heavy smoker; chronic Bronchitis. Pneumonitis 2 years ago.
12. G. W.	52	67.5	150	1.78	17	+ + + +	Slightly increased markings.	Moderate smoker; morning cough.

TABLE 2. LUNG VOLUMES AND VENTILATORY FUNCTION

Case	Radiologic Classification	F.V.C. / P.V.C. X100%	T.L.C. / P.T.L.C. X100%	R.V. / T.L.C. X100%	R.V. / P.R.V. X100%	$F.E.V._{0.5}$ / F.V.C. X100%	M.V.C. / P.M.V.C. X100%	Chest Expansion cms.	End-Tidal Alveolar CO_2 Tension m.m. Hg
1. R.E.	+ +	68	112	56	249	65	66	1.8	41.4
2. S.T.	+ +	84	94	3.3	124	63	106	4.5	39.7
3. J.W.	+ + +	72	74	27	78	64	105	2.5	38.0
4. J.E.	+ + + +	61	69	34	94	60	63	2.2	39.5
5. G.F.	+ + + +	57	78	45	140	70	86	2.0	42.0
6. H.B.	+ + + +	78	92	36	133	59	98	2.2	37.6
7. M.T.	+ + + +	92	101	31	127	65	99	3.0	41.9
8. O.R.	+ + + +	68	76	33	100	67	101	3.4	41.6
9. P.T.	+ + + +	73	80	31	100	59	80	1.8	39.9
10. J.M.	+ + + +	66	79	37	118	64	72	1.6	40.3
11. S.B.	+ + + +	62	95	51	193	53	61	1.8	43.0
12. G.W.	+ + + +	91	94	26	99	63	103	3.0	42.3
Mean		72.7	87.0	36.7	129.6	62.7	86.7	2.48	40.6
S.D.		± 11.27	± 12.8	± 9.2	± 45.5	± 3.9	± 17.5	± 0.83	± 2.71

F. V. C. Forced Vital Capacity
P. V. C. Predicted Vital Capacity
T L. C. Total Lung Capacity
R. V. Residual Volume
P. R. V. Predicted Residual Volume
$F. E. V._{05}$ Forced Expiratory Volume in 0.5 seconds
M. V. C. Maximum Ventilatory Capacity
P.M.V.C. Predicted Maximum Ventilatory Capacity

TABLE 3. VENTILATION AND PULMONARY GAS EXCHANGE.

Case	Radiologic Classification	Hb Gm.	Haematocrit	CO_2 Content mM/ Litre	Arterial p CO_2 m.m. Hg	pH	Whole Blood Buffer Base m. eg./L	O_2 Capacity Vol. %	O_2 Content Vol. %	O_2 Sat. %	Arterial p O_2 m.m. Hg
1. R.E.	+ +	15.4	43	26.0	39.5	7.43	50.0	20.10	19.05	94.7	76
2. S.T.	+ +	14.4	43	25.4	38.0	7.43	50.5	17.30	16.60	96.0	85
3. J.W.	+ + +	9.6	33	24.2	37.0	7.43	48.0	12.70	12.20	96.0	88
4. J.E.	+ + + +	14.0	42	30.1	43.0	7.44	53.0	18.50	17.80	96.2	87
5. G.F.	+ + + +	13.8	42	26.7	42.0	7.40	48.0	18.45	17.70	95.9	88
6. H.B.	+ + + +	9.2	34	23.4	37.0	7.42	46.5	11.55	10.70	92.6	67
7. M.T.	+ + + +	16.9	48	26.7	39.5	7.44	51.5	21.55	20.50	95.1	78
8. O.R.	+ + + +	12.5	40	27.7	40.0	7.45	52.0	14.05	13.55	96.4	88
9. P.T.	+ + + +	13.1	40	24.8	39.0	7.42	49.0	17.90	17.30	96.6	93
10. J.M.	+ + + +	12.5	38	27.0	39.0	7.46	50.0	16.90	15.95	94.4	71
11. S.B.	+ + + +	12.9	42	25.6	41.0	7.39	47.0	17.05	16.30	95.6	85
12. G.S.	+ + + +	13.1	41	26.1	40.5	7.42	48.0	16.20	15.55	95.9	86
Mean		13.11	40.5	26.14	39.6	7.427	49.5	16.85	16.11	95.5	82.7
S.D.		±2.26	±4.04	±1.77	±2.48	±0.016	±2.4	±2.93	±2.79	±0.85	±8.4

*Normal value breathing room air less than 12 m.m. Hg. A-a gradient - Alveolar-Pulmonary Capillary Gradie

#Normal value less than 0.3

M.V. = Minute Volume; $\dot{V}_A$ = Alveolar ventilation; V_T = Tidal Volume; V_D = Physiological Dead Space.

EXCHANGE. ROOM AIR BREATHING.

O_2 t. %	Arterial p O_2 m.m. Hg	Alveolar p O_2 m.m. Hg	A-a* gradient m.m. Hg	M.V. Litres/ Min.	Resp. Rate. Breaths per minute	$\dot{V}_A$ Litres/ min/ sq. m.	V_T ml.	V_D ml.	$\frac{V_D}{V_T}$ #	Resp. Quotient
.7	76	88	12	6.91	11.0	2.47	628	196	0.31	0.85
.0	85	92	7	9.52	16.0	3.36	595	215	0.34	0.79
.0	88	95	7	10.16	17.0	3.24	607	208	0.34	0.92
.2	87	89	2	9.93	14.0	2.85	709	331	0.47	0.96
.9	88	91	3	8.33	20.3	2.99	410	175	0.43	0.78
.6	67	94	27	7.32	19.0	2.21	385	186	0.48	0.81
.1	78	93	15	9.97	12.0	2.83	833	369	0.44	0.87
.4	88	88	0	9.95	17.0	3.05	585	281	0.48	0.82
.6	93	91	-2	10.01	10.0	3.09	1,000	327	0.33	0.80
.4	71	94	23	6.96	11.3	2.66	616	212	0.34	0.83
.6	85	87	2	13.00	21.0	2.17	414	225	0.54	0.82
.9	86	91	5	6.67	7.5	2.47	888	304	0.34	0.88
.5	82.7	91.0	8.4	9.061	14.67	2.78	639	252	0.403	0.844
.85	±8.4	±3.22	±8.8	±1.822	±5.25	±0.47	±185	±75	±0.078	±0.060

pillary Gradient of Oxygen

Space.

TABLE 4. PULMONARY GAS EXCHANGE

ON LOW OXYGEN AND 100% OXYGEN BREATHING

Case	Radiologic Classification	O_2 Capacity Vol. %	BREATHING LOW OXYGEN						BREATHING 100% OXYGEN		
			O_2 in inspired gas %	O_2 Content Vol. %	Sat. %	Arterial p O_2 m.m. Hg	Alveolar p O_2 m.m. Hg	A-a gradient m.m. Hg	O_2 Content Vol. %	Sat. %	Dissolved O_2 nl. %
1. R.E.	+ +	20.1	10.52	14.55	72	35	40	5	21.8	100	1.7
2. S.T.	+ +	17.3	11.52	12.2	71	35	43	8	18.2	100	0.9
3. J.W.	+ + +	12.7	11.80	9.6	76	39	38	-1	14.6	100	1.9
4. J.E.	+ + + +	18.5	11.52	14.1	76	38	39	1	19.7	100	1.2
5. G.F.	+ + + +	18.45	10.47	12.7	69	32	37	5	20.4	100	1.95
6. H.B.	+ + + +	11.55	14.24	8.7	75	38	40	2	13.2	100	1.65
7. M.T.	+ + + +	21.55	11.52	15.5	72	33	31	-2	23.4	100	1.85
8. O.R.	+ + + +	14.05	11.52	11.1	79	40	42	2	15.4	100	1.35
9. P.T.	+ + + +	17.9	11.25	12.5	70	35	32	-3	19.3	100	1.40
10. J.M.	+ + + +	16.9	10.44	10.7	63	28	32	4	18.4	100	1.70
11. S.B.	+ + + +	17.05	10.44	11.95	70	34	33	-1	18.4	100	1.35
12. G.W.	+ + + +	16.2	11.52	11.25	69	33	34	1	17.75	100	1.55
Mean		16.85		12.1	71.8	35.0	36.7	1.7	18.40	100	1.54
S.D.		± 2.97		± 2.48	± 4.4	± 3.35	± 4.8	± 3.37	± 3.11		± 0.32

DISCUSSION

The most striking findings in this study are:

1. Consistently reduced vital capacity.
2. Consistently increased physiological dead-space.
3. Absence of any significant defect of pulmonary gas exchange.

In this series of twelve patients, recurrent respiratory infection was observed in one instance only (Case 11). This patient was a heavy smoker and had definite evidence of chronic bronchitis. This finding is in agreement with recent reports which conclude that ankylosing spondylitis is not associated with an increased incidence of pulmonary infections.[55, 59] It is noteworthy that Bergofsky[8] and his group observed recurrent pulmonary infection in only one patient in a recent study of twenty seven patients with kyphoscoliosis.

The reduction in vital capacity observed in all patients reflects the restriction of chest wall movement due to involvement of the thoracic spine and costovertebral joints in the disease process. The mean value of 72.7% in this series correlates closely with that observed by other workers. Rogan,[46] Needham, and McDonald found the mean value to be 66% in twenty five untreated cases of advanced ankylosing spondylitis. Travis and his group reported a mean value of 71.5% in eleven subjects with ankylosing spondylitis who had received orthopaedic treatment.

Forestier[20] suggests there is augmentation of diaphragmatic excursion in ankylosing spondylitis as the vital capacity is only slightly reduced in the presence of marked fixity of the chest wall. He claims that diaphragmatic excursion is distinctly increased on fluoroscopic examination. Hart[29] found diaphragmatic movement to be "full or even apparently increased."

Restriction of chest movement by strapping[12] or by a canvass laced jacket[18] has been found to reduce the vital capacity by about 30%, but no augmentation or impairment of diaphragmatic excursion could be demonstrated.[12] Fluoroscopy was not performed in the present study but as the vital capacity was reduced by 27.3%, a similar reduction to that seen in the above experimental restrictions of chest movement, it is not necessary to postulate increased diaphragmatic excursion. It is concluded that diaphragmatic movement is certainly normal, but probably not increased, in advanced ankylosing spondylitis.

The degree of reduction in total lung volume recorded in these patients was similar to that observed by Rogan, Needham, and McDonald.[46] Travis and his group[55] reported normal total lung volumes in their study, but the majority of their patients had received orthopaedic treatment which resulted in a straightened dorsal curvature; they suggest that their observation of normal total lung volume with a greatly increased residual volume may have been due to differences in position of rib fixation. The ratio of residual volume to total lung volume in the present series was increased to 36.7% due not only to a reduction in vital capacity but also to a slight increase in the absolute residual volume. This finding of an increase in residual volume is in contradiction to that of Rogan[46] but in

agreement with Travis [55] and Girard [22] who found an even higher residual volume than observed here. It should be noted that Rogan's patients were untreated, the patients studied by Travis had received orthopaedic treatment which straightened the dorsal spine, while the patients of the present series received less vigorous postural therapy. From these facts it is suggested that straightening of the thoracic spine in this disease maintains the total lung volume by increasing the residual volume, the vital capacity remaining reduced by about 30% in all circumstances. Whether this artificial maintenance of total lung volume is beneficial or not is a debatable question, since tidal volume exchange at increased resting lung volume is associated with decreased lung compliance and therefore increased work of breathing.

The timed vital capacity was normal in eleven of the twelve patients, and only slightly reduced in Case II who had chronic bronchitis. It is therefore apparent that obstructive airway disease does not occur as a consequence of ankylosing spondylitis. This observation is in agreement with other reports in the literature. [46, 55]

The maximal ventilatory capacity had a mean value of 86.7%, which is greater than that predicted from the timed vital capacity. This is further evidence that there is no airway obstruction in ankylosing spondylitis; these patients can maintain ventilatory capacity relatively well by increased rate of breathing, the defect being purely restrictive.

Increased physiological dead-space was a constant finding and indicates that abnormal ventilation-perfusion relations exist in advanced ankylosing spondylitis, the ventilation-perfusion ratio being increased.

The finding of a normal mean A-a gradient in this series was surprising; only three patients showed increased gradients, all of minimal degree. This combination of reduced vital capacity, increased physiological dead-space and normal or only slightly increased A-a gradient is of great interest.

Renzetti[43] and his group observed increased physiological dead-space in every instance in a study of twelve patients. They studied pulmonary gas exchange on room air breathing in six subjects and found a mean A-a gradient of 22 mm. Hg. It should be noted that only two of their subjects had a gradient of more than 20 mm. Hg; one of the two appeared to be greatly underweight from their table of clinical data and one wonders if some factor other than ankylosing spondylitis was responsible for the increased gradient. They suggest that, in ankylosing spondylitis, under-expansion of the upper portions and overexpansion of the lower portions of the lung is responsible for the increased physiological dead-space and increased A-a gradient. In this series the normal A-a gradient in all cases when breathing low oxygen indicates that diffusion is not impaired. The mean value of 1.55 ml % for the physically dissolved oxygen on pure oxygen breathing indicates that no significant degree of anatomical shunting exists in ankylosing spondylitis. The mild arterial oxygen desaturation observed in three patients must therefore be due to abnormal ventilation-perfusion relations, to alveolar hypoventilation or to a combination of the two. While an increased ratio of ventilation to perfusion existed in all patients, the expected decrease in the arterial pCO_2 was not found; in addition the mild arterial oxygen desaturation is not explainable on the basis of an increase of ventilation in relation to perfusion. From these

facts it is concluded that alveolar hypoventilation coexists with an increased ventilation-perfusion ratio. This necessarily implies that these two abnormalities exist in different portions of the lung as alveolar hypoventilation and alveolar hyperventilation obviously cannot exist in the same alveoli. As diaphragmatic movement is fully maintained and the chest wall is markedly fixed it is concluded that the hyperventilation is of the lower portions of the lungs and the hypoventilation is of the upper portions. This conclusion is in agreement with the suggestion made by Renzetti and his group.[43] It is of interest to compare the effects of ankylosing spondylitis on pulmonary function with those of kyphoscoliosis, another major cause of thoracic deformity.

While kyphoscoliosis is frequently associated with arterial oxygen desaturation and cor pulmonale,[8] it has been known since the time of Hippocrates[1, 52] that kyphoscoliotics may live a normal life span free of pulmonary complications. The cause of the arterial oxygen desaturation in kyphoscoliosis has been attributed to hypoventilation,[19, 28] but Gray[25] concluded that the abnormalities in pulmonary function in kyphoscoliosis were similar to those occurring in emphysema, implying an alteration of ventilation to perfusion as the main defect.[6]

Shaw and Read[50] state that the kyphoscoliotic shows not only alveolar underventilation but also changes of the ratio of ventilation to perfusion. The conclusion from the present study, that both altered ventilation-perfusion relations and alveolar hypoventilation occur in ankylosing spondylitis imply a similarity to the kyphoscoliotic patient but certain important differences are noted. Ankylosing spondylitis does not progress

to severe arterial oxygen desaturation and cor pulmonale has not been reported. Direct measurements on the work of breathing were not made but several observations may be made in this regard from the pulmonary function data, and a comparison made with kyphoscoliosis. Bergofsky and his group state that the work of breathing in kyphoscoliosis is increased, due in the main, to increased elastic resistance of the deformed chest cage. [8] They observed a five fold increase in the work done on the chest bellows when the tidal volume of normal subjects was achieved. They conclude that the rapid shallow breathing in kyphoscoliosis operates to minimize the work and energy cost of breathing, further, that this pattern of breathing results in alveolar hypoventilation due to increased physiological dead space as well as to increased CO_2 production from the respiratory muscles. Observations in this series indicate a different situation than that existing in kyphoscoliosis.

The mean value of oxygen consumption was 259 ml. per minute which suggests that the energy cost of breathing was not increased. The mean respiratory rate was 14.7 breaths per minute, and the mean tidal volume was 639 ml. Although these are little different from the normal, the combination indicates a tendency towards slow deep breathing in ankylosing spondylitis. In six patients the tidal volume was above 600 ml. and the respiratory rates were less than 15 breaths per minute. This pattern of breathing is opposite to that encountered in kyphoscoliosis.

It is suggested that increased work of breathing is not a characteristic feature of ankylosing spondylitis, at least while activity is subdued. This suggestion is supported clinically by the absence of dyspnoea in the great majority of patients.

Travis[43] and his group found normal tissue and airway resistance in their patients but state that the decreased lung compliance observed may have contributed to an increased work of breathing. However as they point out, the decreased lung compliance may have been due to the orthopaedic straightening of the spine resulting in an increased resting lung volume. Such an increase was not present in the patients of this series and it is re-emphasized that orthopaedic straightening of the thoracic curvature may be an iatrogenic cause of an increased work of breathing of some patients.

Finally it is concluded that the well maintained diaphragmatic excursion and relatively normal energy cost of breathing are the main reasons for the absence of pulmonary insufficiency in this disease.

SUMMARY

An investigation of pulmonary function in ankylosing spondylitis was undertaken. Twelve patients were studied, all of whom had advanced ankylosing spondylitis with a mean duration of eighteen years. All subjects were less than sixty years of age and showed no evidence of cardiac disease. The history was obtained and clinical examination performed. Lung volumes and ventilations were studied. Pulmonary gas exchange studies were carried out at three levels of oxygen breathing to evaluate alveolar ventilation, diffusion, intrapulmonary shunting of venous blood and ventilation-perfusion ratios. The results were tabulated and conclusions drawn.

CONCLUSIONS

1. Ankylosing spondylitis is not associated with an increased incidence of respiratory infections.
2. Moderate reduction in vital capacity is a highly characteristic feature and is associated with reduced chest expansion.
3. Increased physiological dead-space occurs consistently and results from underexpansion of the upper and overexpansion of the lower portions of the lung.
4. There is no significant defect of pulmonary gas exchange. A mild, non progressive, arterial oxygen desaturation exists in a minority of cases; CO_2 retention does not occur.
5. There is no progression to pulmonary insufficiency or cor pulmonale.
6. Well maintained diaphragmatic excursion and relatively normal energy cost of breathing are the main reasons for the absence of pulmonary insufficiency.

BIBLIOGRAPHY

1. Adams, F. : The Genuine Works of Hippocrates. Williams and Wilkins Co., 1939, p. 232.

2. Astrup, P. : A Symposium on pH and Blood Gas Measurement. Methods and Interpretation. Woolmer, R. F. (Ed.). J. & A. Churchill Ltd., 1959, p. 81.

3. Austrian, R., McClement, J. H., Renzetti, A. D., Donald, K. W., and Cournand, A. : Clinical and physiologic features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion. The syndrome of "alveolar-capillary block." Amer. J. Med. 11:667, 1951.

4. Baldwin, E. de F., Cournand, A., and Richards, D. W., Jr., : Pulmonary insufficiency : physiological classification, clinical methods of analysis, standard values in normal subjects. Medicine 27 : 243, 1948.

5. Bates, D. V. and Christie, R. V. : Intrapulmonary mixing of helium in health and emphysema. Clin. Sc. 9:17, 1950.

6. Bates, D. V., Knott, J. M. S., and Christie, R. V. : Respiratory function in emphysema in relation to prognosis. Quart. J. Med. 25:137, 1956.

7. Berggen, S. M. : The oxygen deficit of arterial blood caused by non ventilating parts of the lung. Acta Physiol. Scand. 4 : Suppl. 11, 1942.

8. Bergofsky, E. H., Turino, G. M., and Fishman, A. P. : Cardio-respiratory failure in kyphoscoliosis. Medicine 38:263, 1959.

9. Blumberg, B. S. : Bernard Connor's description of pathology of ankylosing spondylitis. Arthritis and Rheum. 1:553, 1958.

10. Blumberg, B., and Ragan, C. : Natural history of rheumatoid spondylitis. Medicine 35:1, 1956.

11. Burrows, H. J. : Discussion on ankylosing spondylitis. Proc. Roy. Soc. Med. 50:427, 1957.

12. Carton, R. W., and Sepp, E. : On taping the chest. Am. Rev. Tuberc. 76:167, 1957.

13. Comroe, J. H., Jr., Forster, R. E., Dubois, A. B., Briscoe, W. A., and Carlsen, E. : The lung. Clinical physiology and pulmonary function tests. The Year Book Publishers, Inc., Chicago, 1955, p. 81.

14. Cruickshank, B. : Pathology of ankylosing spondylitis. Bull. Rheum. Dis. 10:211, 1960.

15. Cruickshank, B. : Histopathology of diarthrodial joints in ankylosing spondylitis. Ann. Rheumat. Dis. 10:393, 1951.

16. David, J. B., and Blair, H. C. : Spurs of calcaneus in Strumpell-Marie disease. J. Bone and Joint Surg. 32 A: 838, 1950.

17. Donald, K. W., Renzetti, A., Riley, R. L., and Cournand, A. : Analysis of factors affecting concentrations of oxygen and carbon dioxide in gas and blood of lungs : Results. J. Appl. Physiol. 4:497, 1952.

18. D'Silva, J. L., Freeland, D. E., and Kazantzis, G. : Performance of patients with ankylosing spondylitis in maximum ventilatory capacity test. Thorax 8:303, 1953.

19. Fishman, A. P. Bergofsky, E. H., Turino, G. M., Jameson, A. G., and Richards, D. W. : Circulation and repiration in kyphoscoliosis. Circulation 14:935, 1956.

20. Forestier, J., Jacqueline, F., Rotesquerol, J. : Ankylosing Spondylitis. Charles C. Thomas, 1956.

21. Gibson, H. J. : Ankylosing spondylitis aetiology and pathology. J. Fac. Radiologists 8:193, 1957.

22. Girard, J., Loayot, P., Sadoul, P., and Graimprey, J. : Effects on ventilation of thoracic rigidity secondary to ankylosing spondylitis. Ann. Rheumat. Dis. 16:159, 1957.

23. Graham, D. C., and Smythe, H. A. : The carditis and aortitis of ankylosing spondylitis. Bull. Rheumat. Disease. 9:171, 1958.

24. Graham, W., and Uchida, I. A. : Heredity in ankylosing spondylitis. Ann. Rheumat. Dis. 16:334, 1957.

25. Gray, F. D. : Kyphoscoliosis and heart disease. J. Chron. Dis. 4:449, 1956.

26. Guest, C. M., and Jacobson, H. G. : Pelvic and extrapelvic osteopathy in rheumatoid spondylitis. Am. J. Roentgenol. 65:760, 1951.

27. Hamilton, K. A. : Pulmonary disease manifestations of ankylosing spondylarthritis. Ann. Int. Med. 31:216, 1949.

28. Hanley, T., Platts, M. M., Clifton, M., and Morris, T. L. : Heart failure of the hunchback. Quart. J. Med. 27:155, 1958.

29. Hart, F. D., Bogdanovitch, A., and Nichol, W. D. : The thorax in ankylosing spondylitis. Ann. Rheumat. Dis. 9:116, 1950.

30. Hart, F. D., and McLagen, N. F. : Ankylosing spondylitis, a review of 184 cases. Ann. Rheumat. Dis. 14:77, 1955.

31. Hart, F. D., Robinson, K. C., Allchin, F. M., and McLagen, N. F. : Ankylosing spondylitis. Quart. J. Med. 18:217, 1949.

32. Hench, P. S., Editor : Ninth Rheumatism Review. Ann. Int. Med. 28:66, 1948.

33. Lefkovits, A. M., and Thomas, J. R. : Rheumatoid spondylitis : Manifestations and management. Ann. Int. Med. 49:89, 1958.

34. Lilienthal, J. L., Jr., Riley, R. L., Proemmel, D. D., and Franke, R. E. : An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. Amer. J. Physiol. 147:199, 1946.

35. Lucherini, T., and Cecchi, E. : Natural history of ankylosing spondylitis. Ann. Rheumat. Dis. 11:337, 1952.

36. Meneeley, G. R., and Kaltreider, N. L. : Volume of the lung determined by helium dilution. J. Clin. Invest. 28:129, 1949.

37. Miller, J. L. : Differential diagnosis between Strumpell-Marie disease and osteoarthritis of the spine. Jour. Lab. and Clin. Med. 22:19, 1936.

38. Miller, W. F., Johnson, R. L., and Wu, N. : Relationships between fast vital capacity and various timed expiratory capacities. J. Appl. Physiol. 14:157, 1959.

39. Mowbray, R., Latner, A. L., and Middlemiss, J. H. : Ankylosing spondylitis. Quart. J. Med. 18:187, 1949.

40. O'Connell, D. : Ankylosing spondylitis, the literature up to the close of the nineteenth century. Ann. Rheumat. Dis. 15:119, 1956.

41. Polley, H. F. : Diagnosis and treatment of rheumatoid apondylitis. M. Clin. North America. 39:509, 1955.

42. Polley, H. F., and Slocumb, C. H. : Rheumatoid spondylitis : a study of 1035 cases. Ann. Int. Med. 26:240, 1946.

43. Renzetti, A. D., Jr., Nicholas, W., Dutton, R. E., Jr., and Jivoff, L. : Some effects of ankylosing spondylitis on pulmonary gas exchange. New England J. Med. 262:215, 1960.

44. Riley, R. L., and Cournand, A. : Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs : theory. J. Appl. Physiol. 4:77, 1951.

45. Riley, R. L., and Cournand, A., and Donald, K. W. : Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs : methods. J. Appl. Physiol. 4:102, 1951.

46. Rogan, M. C., Needham, C. D., and McDonald, I. : Effect of ankylosing spondylitis on ventilatory function. Clin. Sc. 14:91, 1955.

47. Schilder, D. P., Harvey, W. P., and Hufnagel, C. A. : Rheumatoid spondylitis and aortic insufficiency. New England J. Med. 255:11, 1956.

48. Scholander, P. F. : Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. J. Biol. Chem. 167:235, 1947.

49. Severinghaus, J. W. : Oxyhaemoglobin dissocation curve correction for temperature and pH variation in human blood. J. Appl. Physiol. 12:485, 1958.

50. Shaw, D. B., and Read, J. : Hypoxia and thoracic scoliosis. Brit. Med. J. 2:1486, 1960.

51. Singer, R. B., and Hastings, A. B. : Improved clinical method for estimation of disturbances of acid-base balance of human blood. Medicine 27:223, 1948.

52. Snider, G., Miller, B., and Ellisberg, E. : Kyphoscoliotic cardiopulmonary disease. A reappraisal. Am. Rev. Tuberc. 78:325, 1958.

53. Sproule, B. J., Miller, W. F., Cushing, I. E., and Chapman, C. B. : An improved polarographic method for measuring oxygen tension in whole blood. J. Appl. Physiol. 11:365, 1957.

54. Swezey, R. L. Patterson, J., Marcus, S., Strange, D., and Levin, M. H. : Rheumatoid spondylitis : a clinical and socio-economic study. Ann. Int. Med. 47:904, 1957.

55. Travis, D. M., Cook, C. D., Julian, D. G., Crump, C. H., Helliesen, P., Robin, E. D., Bayles, T. B., and Burwell, C. S. : The lungs in rheumatoid spondylitis. Amer. J. Med. 29:623, 1960.

56. Van Slyke, D. D., and Neill, J. M. : The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. 61:523, 1924.

57. Van Slyke, D. D., and Sendroy, J., Jr. : Studies of gas and electrolyte equilibria in blood. Line charts for graphic calculations by the Henderson-Hasselbach equation, and for calculating plasma carbon dioxide content from whole blood. J. Biol. Chem. 79:781, 1928.

58. West, J. R., Baldwin, E. de F., Cournand, A., and Richards, D. W., Jr., : Physiopathologic aspects of chronic pulmonary emphysema. Amer. J. Med. 10:481, 1951.

59. Wilkinson, M., and Bywaters, E. G. L. : Clinical features and course of ankylosing spondylitis. Ann. Rheumat. Dis. 17:209, 1958.

APPENDIX 1

LABORATORY DATA: CALCULATIONS AND EQUATIONS USED

CASE 10. J.M. November 4, 1961.

Age 31 yrs. Height 69.5 inches. Room Temperature 21.5 ^{o} C

Body surface area 1.68 sq. metres. Barometric pressure 709 m.m.Hg.

Lung Volumes and Ventilation

Forced Vital Capacity. (B.T.P.S.)

Observed values:	2,780 ml.
	2,750 ml.
	2,810 ml.
Recorded value	2,810 ml.

Residual Volume . (B.T.P.S.)

Observed values	1,615 ml.
	1,670 ml.
Recorded value	1,670 ml.

Total Lung Capacity. (B.T.P.S.)

Highest values of residual volume and forced vital capacity used.

2,810 ml. + 1,670 ml. = 4,480 ml.

Forced Expiratory Volume $_{0.5 \text{ seconds}}$ (B.T.P.S.)

Observed values	1,800 ml.
	1,760 ml.
	1,780 ml.

Recorded value 1,800 ml. = 64% of the forced vital capacity

Maximum Ventilatory Capacity (B.T.P.S.)

Observed values over 15 second intervals 21.25 litres

18.90 litres

19.94 litres

Recorded value 21.25 litres/15 seconds = 85 litres/minute

Chest Expansion

Measured value at 4th intercostal space 1.8 cms.

End-Tidal Alveolar CO_2 Tension

Observed values 41.4 m.m.Hg.
41.3 m.m.Hg.

Recorded value 41.4 m.m.Hg.

Pulmonary Gas Exchange

Room Air Breathing

Inspired Air	Expired Air
$F_I O_2$ 0.2094	$F_E O_2$ 0.1652
$F_I CO_2$ 0.0003	$F_E CO_2$ 0.0386
$F_I N_2$ 0.7903	$F_E N_2$ 0.7962

Respiratory Rate = 11.3/minute. Volume of Expired Air = 24.55 litres

Time of collection = 4 minutes.

$\dot{V}_E$ ATPD = $\frac{24.55}{4}$ = 6.14 L/min.

$\dot{V}_E$ STPD = $6.14 \times \frac{709 \times 273}{295 \times 760}$ = 5.30 L/min.

$\dot{V}_1$ STPD = $5.30 \times \frac{0.7962}{0.7903}$ = 5.34 L/min.

$\dot{V}_1$ BTPS = $5.34 \times \frac{760 \times 310}{662 \times 273}$ = 6.96 L/min.

$\dot{V}O_2$ = (5.34 x 0.2094) - (5.30 x 0.1652) = 243 ml./min.

$\dot{V}CO_2$ = (5.30 x 0.0386) - (5.34 x 0.0003) = 202 ml./min.

Respiratory Quotient = $\frac{202}{243}$ = 0.83

Astrup pH Meter

Arterial blood pH

Observed values pH	7.458
	7.457
	7.458
Recorded value pH	7.46

Van Slyke Manometric Apparatus

Arterial Carbon Dioxide Content

Observed values	27.03 m.M./litre
	26.94 m.M./litre
Recorded value	27.0 m.M./litre

Arterial Carbon Dioxide Tension

Using the Van Slyke and Sendroy Chart [57]

Measured value 39.0 m.m.Hg.

Whole Blood Buffer Base

Using the Singer-Hastings nomogram [51]

Measured value 50.0 m.M./litre

Arterial Oxygen Content

Capacity.

Observed values	16.94 vol.%
	16.88 vol.%
Recorded value	16.90 vol.%

Content.

Observed values	16.00 vol.%
	15.91 vol.%
Recorded value	15.95 vol.%

Arterial Oxygen Saturation

$$= \frac{15.95}{16.90} \times 100\% = 94.4\%$$

Arterial Oxygen Tension

Using Severinghaus nomogram [49] (Figure 4.)

Measured value = 71 m.m.Hg.

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Alveolar Ventilation [13]

$$\dot{V}_A = \frac{202}{39} \times \frac{310}{273} \times 760 = 4.47 \text{ L/min.}$$

$$V_T = \frac{6.96}{11.3} = 616 \text{ ml.}$$

$$V_D = \frac{39 - (0.0386 \times 662)}{39} \times 616 = 212 \text{ ml.}$$

(From Bohr's Equation [13])

Alveolar Oxygen Tension

Inspired Oxygen Tension = 0.2094×662 = 139 m.m.Hg.

$$\text{Alveolar Oxygen Tension} = 139 - 39 \left(0.2094 - \frac{(1 - 0.2094)}{0.83}\right) = 94 \text{ m.m.Hg}$$

(Alveolar Air Equation [13])

Alveolar - arterial Oxygen Gradient

= 94 - 71 m.m.Hg. = 23 m.m.Hg.

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APPENDIX 2

ERRORS OF METHODS AND THEIR SIGNIFICANCE

Godart Pulmotest

Errors in the measurement of lung volumes and ventilation using the Godart Pulmotest can arise from two sources

1. The error of the instrument and operator.
2. The inconsistency of performance by the patient.

Vital Capacity

The following are data obtained from a trained subject (J.M.) with no evidence of lung disease.

Measured values of vital capacity (ml.)

4350	4440	4485	4560
4380	4440	4500	4560
4395	4470	4560	4575
4440	4470	4560	4575

The range of values is 225 ml., giving an approximate error of $\pm$ 110 ml.

A subject who was not familiar with the test (S.G.) and who showed no evidence of airway obstruction was tested twelve times and the range was slightly larger, being 260 ml. The calculated error here is in the region of $\pm$ 130 ml.

Considering the facts that the patients in this series showed no evidence of airway obstruction (Except Case II) and that values for the vital capacity were required to approximate within 50 ml., the error of ± 130 ml. was regarded as a satisfactory value.

Residual Volume

The following values were obtained from a subject (S.G.) who showed no evidence of lung disease.

Measured values of residual volume (ml.)

1,065	1,115
1,090	1,140
1,110	1,190

These values show a range of 125 ml., giving an approximate error of ± 65 ml. Using the same considerations as in estimating the error of vital capacity, an error of ± 65 ml. was regarded as a suitable value for this study.

Total Lung Capacity

The error in calculating total lung capacity was taken as the sum of the errors for vital capacity and residual volume. The estimated error used was therefore ± 195 ml.

Forced Expiratory Volume $_{0.5}$ seconds

The following values were obtained from a subject (S.G.).

Measured values of F.E.V.$_{0.5}$ (ml.)

2790	2835
2805	2835
2820	2880

These values show a range of 90 ml., giving an approximate error of $\pm$ 50 ml. In this study only those consecutive results which agreed within 50 ml. were used. An error of $\pm$ 50 ml. was therefore regarded as a suitable estimate for this test.

W. F. Miller [38] defines a reduction in F.E.V.$_{05}$ as being a value less than 60% of the forced vital capacity. While there may be variations in this value between subjects of different location and race, this definition was arbitrarily chosen for the present study.

Maximum Ventilatory Capacity

The following values were obtained from Case 9 of the present series.

M.V.C. in L/min.	115	105
	112	101
	106	96

The range of these values is 19L./minute, giving an approximate error of ± 10 L./minute. As this test is carried out over 15 second - 30 second intervals and requires maximum effort of the patient, great variability can occur from one day to another and the error becomes larger. The observed error of ± 10 L./minute was not regarded as realistic for the test over a series of patients, and an error of ± 20 L./minute was arbitrarily chosen.

Van Slyke Manometric Apparatus

Arterial Oxygen Content

The following values were obtained from one sample of femoral artery blood (Subject S.H.)

Arterial oxygen content. Vol %

16.70	16.84
16.79	16.91
16.82	

The range of these values is 0.22 vol.%, and the approximate error is ± 0.1 vol.%.

Carbon Dioxide Content.

The error of the method was estimated from a series of six consecutive arterial blood samples which were run in duplicate.

The values obtained were as follows. (m.M./Litre.)

Value A	Value B	Variation
25.85	25.62	0.23
23.03	22.79	0.24
22.09	21.86	0.23
22.33	22.09	0.27
22.79	21.86	0.07

These values have a maximum range of 0.27 m.M./Litre. From these results the maximum error of the method was estimated at $\pm$ 0.2 m.M./Litre.

Astrup pH Meter

The instrument was calibrated using two certified primary buffers (U.S. Bureau of Standards and British Standards Institution) whose pH was given to the third decimal place. The error of the instrument was arbitrarily set at $\pm$ 0.01 units of pH despite the fact that duplicate readings were always within a narrower range than 0.02 units.

Errors of Other Instruments

The errors of the Scholander gas analyzer and the Beckman Oxygen analyzer were very small and it was calculated that the error of these instruments made less than a 1% difference to the final values obtained in the pulmonary gas exchange studies. For

this reason these errors are neglected in the discussion of the significance of errors of methods used.

Calculation of the Arterial p CO_2

Calculation is from the Van Slyke and Sendroy charts. As the error of the CO_2 content is $\pm$ 0.2 m.M./Litre. and the error of arterial pH $\pm$ 0.01 units the range of error for the arterial p CO_2 was measured at 2 m.m.Hg. This gives an approximate error of $\pm$ 1 m.m.Hg.

Calculation of the Arterial p O_2

From the Severinghaus nomogram [51] it is observed that the largest error in reading the arterial p O_2 arises in the 95 - 100 % oxygen saturation range. Fortunately none of the patients of this series had a saturation of greater than 96.7% which enabled the nomogram to be used satisfactorily in all cases.

The error of $\pm$ 0.1 vol.% for the Van Slyke oxygen content determination gives approximately a $\pm$ 0.6% error in determining the percentage oxygen saturation at the level observed in these patients. From the nomogram it was calculated that the error of estimating the arterial p O_2 is therefore $\pm$ 5 m.m.Hg.

Calculation of the Alveolar p CO_2

Assuming the validity of the alveolar air equation [13] the

main source of error in determining the alveolar p CO_2 is the arterial p CO_2 measurement. The error of the arterial p CO_2 was estimated at $\pm$ 1 m.m.Hg.; for the range of values obtained this is a 2 1/2% error. From the alveolar air equation the error in estimation of the alveolar p CO_2 was calculated to be $\pm$ 3 m.m.Hg.

Calculation of the A-a. Gradient.

As the error in determining the arterial p O_2 is $\pm$ 5 m.m.Hg. and the error of the alveolar p O_2 is $\pm$ 3 m.m.Hg., it is therefore estimated that the error in determining the A-a. gradient is $\pm$ 8 m.m.Hg.

Calculation of the Dissolved Oxygen Content

The dissolved oxygen content is obtained by subtracting the oxygen capacity value from the oxygen content value when breathing 100% oxygen. As the error of each Van Slyke measurement is 0-1 vol.%, the error of the dissolved oxygen content is 0.2 vol.%.

Calculation of the Physiological Dead-Space

The error of this value depends mainly upon the determination of the arterial p CO_2 and the tidal volume. The error of the arterial p CO_2 is $\pm$ 1 m.m.Hg. The error of the tidal volume value is very small as the respiratory rate was monitored

and recorded throughout the collection of the expired air for a four minute period. The estimated error of the value for physiological dead-space was calculated to be ± 10 ml. In calculation of the ratio of the physiological dead-space to tidal volume an error of - 5% of the value obtained was estimated.

Calculation of the Ratio of Residual Volume to Total Lung Capacity

The estimated error of this value was calculated to be approximately 10% of the value obtained for the ratio; for example a determined ratio of 30% should be regarded as (30 ± 3)%.

SIGNIFICANCE OF THE ERRORS OF METHODS

The validity of the results of this study depends upon the errors of the techniques employed and the statistical significance of the values obtained; these factors being of crucial importance in a small series of twelve patients.

Forced Vital Capacity

The mean value of 72.7% and the P value of less than 0.001 are little affected by the ± 130 ml. error of determination. It is concluded that moderate reduction of vital capacity is a highly characteristic feature of this series.

Residual Volume

The normal value for the residual volume was taken as 25%

of the predicted normal total lung volume. This method for predicting the residual volume has definite limitations as in normal persons the residual volume can vary between 20% and 35% of the total lung volume, and therefore the mean normal value of 25% applies to a large population rather than to the individual. The mean value obtained in these patients was 129.6% with the large standard deviation of ± 45.5. The P value of 0.06 is above the defined limit for significance. The variability of the normal value for residual volume, the error of determination, and the small number of cases in other reported studies [46, 55] must be carefully considered in evaluating the problem of residual volume in ankylosing spondylitis.

Total Lung Capacity

The maximum experimental error of ± 195 ml. represents approximately a 5% error in the results obtained and does not appreciably alter the significance of the mean value of 87% (P = 0.01). Variability of the normal value must be considered however and this series is too small for precise conclusions to be drawn.

Ratio of Residual Volume to Total Lung Capacity

The mean value was 36.7% with a standard deviation of ± 9.2 and the P value was 0.2. As the normal residual volume ranges from 20% to 35% it is apparent that the mean value is not

significantly increased and a much larger number of patients would have to be studied to assess the frequency and degree of abnormalities of this ratio.

Maximum Ventilatory Capacity

The estimated error of ± 20 L./minute in determination of the maximum ventilatory capacity is of importance in evaluation of these results, as this error is of the approximate magnitude of the mean decrease observed. The mean value of 86.7% has a standard deviation of 17.5 and the P value is less than 0.02. The observed value is in agreement with that of other reports [46,55] however, and it is probable that the slight reduction in maximum ventilatory capacity observed here did in fact exist in these patients.

Physiological Dead-Space

The experimental error of ± 10 ml. does not appreciably affect the results obtained and does not affect the calculated ratio of the physiological space to tidal volume to any significant degree. The ratio of physiological dead-space to tidal volume was above the normal upper limit of 0.3 in every patient and as the error of the method is only ± 5% this finding is regarded as an important and consistent feature of the series.

Alveolar - arterial Oxygen Gradient

The estimated maximum error of ± 8 m.m.Hg. for the A-a

gradient determination does not appreciably alter the results obtained in these patients. The mean value for the gradient was 8.4 m.m.Hg. on room air breathing with a standard deviation of 8.8 m.m.Hg. In no instance was the gradient above 27 m.m.Hg. and ten patients had gradients of 12 m.m.Hg. or less. This is a very striking finding in view of the fact that all twelve patients had moderate or severe restriction of chest expansion.

The experimental error of 8 m.m.Hg. accounts for the negative gradients observed in several instances in the study, and it is possible that the finding of a gradient above 20 m.m.Hg. in two patients was also due to the error of the method. If the maximum experimental error of 8 m.m.Hg. was added to every A-a gradient on room air breathing the mean value would be 16.4 m.m.Hg. which is close to the upper limit of normal set by some workers.[13]

APPENDIX 3

STATISTICAL DATA

The mean value and standard deviation were calculated for all results and are shown in Tables 2-4. The t test was applied to all results in which deviation from the predicted normal values were suspected.

Statistical significance is defined as the calculated P value being less than 0.05.

Pulmonary Function Test	t	n	P
Vital Capacity	8.25	11	Less than 0.001
Total Lung Capacity	3.42	11	Less than 0.01
Residual Volume	2.16	11	0.06
$\frac{\text{Residual Volume}}{\text{Total Lung Volume}}$	1.31	11	0.2
Chest Expansion	13.2	11	Less than 0.001
Maximum Ventilatory Capacity	2.9	11	Less than 0.02